IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: Appeal to the Board of Patent Appeals and Interferences

PATENT APPLICATION

AF

1600

In re PATENT APPLICATION of
Inventor(s): Riethmuller-Winzen et al.
Appln. No.: 09 (Series Code ↑) | 666,146 (Serial No. ↑)

Group Art Unit: 1617
Examiner.: Hui, San Ming R.
Atty. Dkt. P 0268411 (M#) | 99/16 PH/Ba (Client Ref)

Filed: September 21, 2000
Title: Method for the therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and fallopian tube obstruction

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Date: May 5, 2003

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Hon. Commissioner for Patents
PO Box 1450
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Sir:

1. ☐ **NOTICE OF APPEAL**: Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision (not Advisory Action) dated _____ of the Examiner twice/finally rejecting claim(s) in this application or in this application and its parent application.
2. ☒ **BRIEF** on appeal in this application attached in triplicate (extendable up to 5 months).
3. ☐ An **ORAL HEARING** is respectfully requested under Rule 194 (due two months after Examiner's Answer- unextendable)
4. ☐ Reply Brief is attached in triplicate (due two months after Examiner's Answer – unextendable).
5. ☐ "Small entity" statement filed: ☐ herewith. ☐ previously.

6. ☐ Fee NOT required because paid in prior appeal in which the Board of Patent Appeals and Interferences did not render a decision on the merits (35 USC 134).

7. **FEE CALCULATION**

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8. Original due date: December 3, 2002				
9. Petition is hereby made to extend the original due date	(1 mo)	$110/$55		115/215
to cover the date this response is filed for which the	(2 mos)	$410/$205		116/216
requisite fee is attached.	(3 mos)	$930/$465		117/217
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10. Enter any previous extension fee paid ☐ previously since above				
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11. **Subtract line 10 from line 9 and enter: Total Extension Fee**			+$1970	
12. **TOTAL FEE =**			$2290	

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fee on Brief

U.S. Application No.: 09/666,146

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re PATENT APPLICATION OF:

Riethmuller-Winzen et al.

Group Art Unit: 1617

Appln. No.: 09/666,146

Examiner: Hui, San Ming R.

Filed: September 20, 2000

Title: METHOD FOR THE THERAPEUTIC MANAGEMENT OF EXTRAUTERINE PROLIFERATION OF ENDOMETRIAL TISSUE, CHRONIC PELVIC PAIN AND FALLOPIAN TUBE OBSTRUCTION

#16
HKD
5-15-03

BRIEF ON APPEAL

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01 FC:1255 1970.00 CH
02 FC:1402 320.00 CH

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Date: May 5, 2003

I. INTRODUCTION

This appeal is from an official action dated April 4, 2002, finally rejecting claims 1-13 and 28-31 of the above-identified patent application.

A. Real Party in Interest

The real party in interest for this appeal and the present application is Zentaris AG by way of an assignment recorded in the U.S. Patent and Trademark Office at Reel 012752, Frame 0016.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences known to the appellant, the appellant's representatives or the assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

C. Status of Claims

Claims 1-13 and 28-31 are pending, stand rejected, and are on appeal. The claims on appeal are set forth in the attached Appendix. Claims 1 and 2 are independent, claims 3-13 depend from claim 1, claim 28 depends from claim 2, claim 29 depends from claim 28, claim 30 depends from claim 3, and claim 31 depends from claim 8.

D. Status of Amendments

All claim amendments have been entered of record.

II. SUMMARY OF THE INVENTION

Claim 1 is directed to a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction, the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, whereby subsequently the administration of the LHRH antagonist is ceased.

Claim 2 is directed to a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction, the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, wherein the LHRH antagonist is administered in a dosage to achieve the estrogen serum concentration level between about 35 pg/ml and about 80 pg/ml, whereby subsequently the administration of the LHRH antagonist is ceased.

Claim 3 further defines the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive.

Claim 4 further defines the method of claim 1 where the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

Claim 5 further defines the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

Claim 6 further defines the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

Claim 7 further defines the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, a non-steroidal anti-rheumatic agent, an analgesic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

Claim 8 further defines the method of claim 1 wherein the LHRH antagonist is administered starting in the early to mid follicular phase.

Claim 9 further defines the method of claim 1 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2 LRHR antagonist.

Claim 10 further defines the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly does of about 3 to 10 mg per week.

Claim 11 further defines the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily does of about 0.25 mg to 0.5 mg/day.

Claim 12 further defines the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month.

Claim 13 further defines the method of claim 1 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

Claim 28 further defines the method of claim 2 wherein said estrogen serum concentration level is between about 45-75 pg/ml.

Claim 29 further defines the method of claim 28 wherein said estrogen serum concentration level is about 50 to about 75 pg/ml.

Claim 30 further defines the method of claim 3 wherein said contraceptive is an oral contraceptive.

Claim 31 further defines the method of claim 8 wherein the LHRH antagonist is administered on cycle day one to three.

III. ISSUES AND REJECTIONS

In the final official action dated April 4, 2002, claims 1-13 and 28-31 were rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,663,145 in view of U.S. Patent No. 5,658,884 and Nachtigall *et al.* (Danforth's Obstetrics and Gynecology, Chapter 41, 1994, pg. 757-769).

Thus, the issues on appeal are whether claims 1-13 and 28-31 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,663,145 in view of U.S. Patent No. 5,658,884 and Nachtigall *et al.*

IV. GROUPING OF CLAIMS

Each claim of this patent application is separately patentable and upon issuance of a patent will be entitled to a separate presumption of validity under 35 U.S.C. § 282. For convenience in handling of this appeal, the claims are grouped as follows:

Group I, claims 1, 3-13, 30, and 31; and

Group II, claims 2, 28, and 29.

Each of Groups I and II will be argued separately in the following arguments. The groups do not stand or fall together. In addition, the claims within each Group do not stand or fall together and are argued separately in the following arguments.

V. ARGUMENT

A. The Law Regarding Factual Inquires to Determine Obviousness/Non-Obviousness

Several basis factual inquires must be made to determine obviousness or non-obviousness of patent application claims under 35 U.S.C. § 103. These factual inquires are set forth in Graham v. John Deere Co., 383 US 1, 17, 148 USPQ 459, 467 (1966);

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at

> issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined.

As stated by the Federal Court in In re Ochiai, 37 USPQ 2d 1127, 1131 (Fed. Cir. 1995);

> [T]he test of obviousness *vel non* is statutory. It requires that one compare the claim's subject matter as a whole with the prior art to which the subject matter pertains. 35 U.S.C. § 103.
> The inquiry is thus highly fact-specific by design . . . When the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) (Emphasis added).

In rejecting claims under 35 U.S.C. § 103(a), an Examiner bears an initial burden of presenting a *prima facie* case of obviousness. A *prima facie* case of obviousness is established only if there is a suggestion or motivation to combine reference teachings; a reasonable expectation of success; and the prior art references, when combined, teach or suggest all the claim limitations. If an Examiner fails to establish a *prima facie* case, a rejection is improper and will be overturned. See In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). "If examination . . . does not produce a *prima facie* case of unpatentability, then without more, the Applicant is entitled to the grant of the patent." In re Oetiker, 977 F.2d 1443, 1445-1446, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

B. Rejections Under 35 U.S.C. § 103(a)

The examiner rejected claims 1-13 and 28-31 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,663,145 (hereinafter Engel '145 in view of U.S. patent No. 5,658,884 (hereinafter Hodgen '884) and Nachtigall *et al.*

The examiner asserted that Engel '145 teaches (1) a method of administering the LH-RH antagonist, Cetrorelix, in two phases, to a patient for treatment of endometrial hyperplasia, and (2) that the dosages of Cetrorelix useful in the method is 1 gm to 60 mg. The examiner then asserted (again) what the cited primary reference does **not** teach: (1)

expressly teach the use of other agents in the method of treating endometrial hyperplasia; (2) expressly teach that the administration of the LH-RH antagonist causes the estrogen serum level to be 45-75 pg/ml or 50-75 pg/ml; (3) expressly teach the time and the frequency of Cetrorelix administration; and (4) expressly teach the LH-RH antagonist to be administered on cycle day one to three.

The examiner then referenced the first secondary reference, Hodge '884, asserting that the issued U.S. patent teaches administration of an LH-RH antagonist in a method of treating endometriosis such that the estrogen level would be between 35-50 pg/ml. With respect to the second secondary reference. Nachtigall *et al.*, the examiner asserted that the cited document teaches Danazol (an isoxazol derivative of 17-alhpa-ethinyl testosterone, oral contraceptives, NSAIDS and other analgesics are useful in treating endometriosis.

In sum, the examiner asserted that it would have been obvious to employ Cetrorelix and other agents herein for a method to treat endometriosis. The examiner further stated that it is *prima facie* obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose.

1. Claim 1 is Not Obvious In View of The Cited Documents

The Appellants submit that, during prosecution on the merits, the examiner failed to present a *prima facie* case of obviousness under 35 U.S.C. §103(a). It is the Appellants' position that that Engel '145, either alone or in combination with Hodgen '884 and/or Nachtigall *et al.* fail to teach or suggest the appellants' presently claimed invention (*i.e.*, fails to teach or suggest all of the claim limitations) of a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

The primary reference, Engel'145, simply discloses a kit comprising an initial dose of an LH-RH antagonist suitable for treatment of hormone dependent conditions, and at least one maintenance dose of the LH-RH antagonist. The kit is suitable for a combination treatment regiment in which an initial dose is followed by several maintenance doses. In contrast, the claimed invention is directed to a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

As admitted to by the examiner, Engel '145 does **not** specify either the time period or frequency of administration or the amounts of the LH-RH antagonist to achieve the estrogen serum level of between 35 and 80 pg/ml nor does the cited document teach or suggest any follow-up treatment or therapy with progestine/gestagens or androgens for further prevention of ovulation besides menstrual and endometrial bleeding to avoid re-occurrence of symptoms or new endometric. Additionally, an immediate follow-up therapy with non-steroidal anti-rheumatic agents or analgesics is also not disclosed or suggested in Engel '145.

The first secondary reference, Hodgen '884 does nothing to cure the deficiencies of Engel '145. The examiner cited Hodgen '884 as teaching administration of the GnRH antagonist such that the estrogen level between 35 and 45 pg/ml is achieved. Hodgen '884 actually **does** disclose that a 24 hour serum estradiol level in the range of 35 to 45 pg/ml can be achieved in monkeys by administering LH-RH antagonist. However, Hodgen does not give any dose range of the LH-RH antagonist. The dose has to be determined according to the results of an expensive and time consuming progesterone challenge test.

Furthermore, unlike the presently claimed invention (*i.e.*, short term induction), Hodgen '884 is directed to long-term treatment intervals, such as a number of years of

therapy. See column 9, lines 3-6. The teachings of Hodgen '884 simply do not teach or suggest applicability of the long-term treatment study conducted on primates to a short-term induction treatment period. There is no teaching or suggestion from Hodgen '884 that an effective therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction may be achieved by a short 4-to 12 week induction treatment. Moreover, similarly to Engel '145, Hodgen '884 does not disclose any follow-up therapy.

In view of the foregoing, it is submitted that Engel '145 and Hodgen '884, either alone or in combination, neither teach nor suggest a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

The examiner further cited Nachtigall *et al.* as teaching use of Danazol, an oral contraceptive, for treatment of endometriosis. Once again, nothing in this reference suggests the claimed method, involving administering to a patient of LH-RH antagonist for a short-term induction period. Furthermore, while Danazol is useful in treating endometriosis, due to the occurrence of severe side effects, it is common knowledge that treatment of endometriosis with Danazol has been largely abandoned nowadays.

Oral contraceptives do not cure endometriosis. As disclosed on page 766, column 1, last paragraph of Nachtigall *et al.*, "there are few data to support the use of this class of drugs. No controlled or comparative trials have been performed to confirm efficacy, making this treatment approach at least acceptable of the medical therapies available." The reference, therefore, teaches away from use of oral contraceptives in treatment of endometriosis.

Non-steroidal anti-rheumatic agents and analgesics are discussed for the treatment of pain as well as of inflammation. *e.g.,* of patients with chronic adhesions or with low grade stages of the disease. These agents are not effective in curing patients with severe or chronic endometriosis, not even in the short term.

The examiner further states that it is *prima facie* obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose. It is well known in the art of therapeutic treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known for the same purposes. Combination of pharmaceuticals often leads to serious side effects due to their potential interaction. Moreover, as discussed above, the invention is not directed to a combinatorial treatment, but rather to a follow-up treatment, and, therefore, the reasons for combining agents given by the examiner are simply not applicable to the claimed invention.

Also, according to the examiner's statement, optimization of parameters, such as dosage range, dosage frequency, and timing is obvious as being within the skill of the artisan. While routine minor adjustments of dosage and its frequency may well be within the skill of an ordinary artisan, reduction of treatment time from years of therapy as taught by the references to a maximum of three month periods, as claimed in the instant invention, can hardly fall within the meaning of "optimization." In fact, modifying the treatment regiments disclosed in the cited references to shorten them to 4 to 12 week induction treatments would render the treatment regimens disclosed in Engel '145 and Hodgen '884 unsatisfactory and non-useful for the intended therapeutic treatments.

It is, therefore, submitted that the references alone or in combination do not suggest the claimed therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH

antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment with subsequent termination of LH-RH antagonist administration.

The examiner admitted that Engel '145, the primary reference, teaches a two phase treatment of endometrial hyperplasia, using a dosage of 1 mg to 60 mg. The examiner also admitted that Engel '145 fails to teach the claimed time and frequency of cetrorelix administration, the claimed serum estrogen levels, or the follow up treatment with contraceptives, NSAIDs, analgesics, and certain androgens, as claimed. By contrast the claimed treatment is a specified short term regiment, and is not limited to an initial high dose followed by maintenance doses. The present method requires a short term treatment during which serum estradiol levels are kept within the early follicular phase range of 35-80 pg/ml. In short, the examiner admitted that Engel '145 fails, at a minimum, to even suggest the claimed invention, and therefore is severely deficient as a reference for a rejection based upon 35 U.S.C. §103(a).

The examiner contended that a skilled artisan would combine the teachings of Hodgen '884 with Engel '145 to arrive at the claimed short-term therapy. The examiner stated that Hodgen '884 teaches treatment with an LH-RH antagonist for a period up to 97 days, which the examiner asserted is close to the claimed dosing frequency. Although the examiner cited no support in the specification for this assertion, it appears to the Appellants that the examiner is relying on the dosing data set forth in Table 1 of Hodgen '884.

The Appellants submit that the examiner has incorrectly analyzed the experimental data, and has ignored the sentence immediately following Table 1 in column 8, lines 55-58, wherein the data are described as evidence of the "utility of titering individualized GnRH ant [*sic*] doses to amenorrhea, while maintaining tonic ovarian estradiol secretion in a milieu suitable for extended therapeutic regimens." The actual treatment regimen of Hodgen '844, as previously

noted to the examiner, suggests that 6 months is too short, and that a regimen lasting years is desirable.

The claims are not directed to a method requiring pre-therapeutic regimen titering. In fact, the specification teaches that the claimed method does **not** require titering of the dosage of LH-RH antagonists. Thus, it appears that the examiner is employing faulty logic in attempting to maintain the position that Hodgen '884 teaches something "close" to a 4-12 week treatment regimen for endometriosis.

Finally, the examiner continues to assert that a skilled artisan would read Nachtigall *et al.* to mean that various NSAIDs and contraceptives are useful in treating endometriosis. While it is true that Nachtigall *et al.* teaches that oral contraceptives, GnRH analogs and testosterone derivatives are each separately useful in treating endometriosis, the cited document does not teach their combinations in treatment regimens (notwithstanding the fact that the present invention is directed, *inter alia*, to follow-up therapy). To the contrary, Hodgen '884 only teaches that combining surgical and medical (pharmacological) treatments may be desirable in managing the condition. The actual teachings of Nachtigall *et al.* rebut the examiner's assertion that it is *prima facie* obvious to combine the disclosed agents. Perhaps the examiner thinks such combinations are obvious, but those skilled in the art (Nachtigall *et al.*) did not seem to agree with this premise in 1994.

Nachtigall *et al.* does not teach nor suggest the follow up therapy required by the claims, or that more than one medical treatment is desirable. Nachtigall *et al.* certainly does not supplement the deficiencies of the combined teachings of Engel '145 and Hodgen '884 with respect to the claimed short-term treatment regimen administering an LH-RH antagonist for a period of about 4 to 12 weeks.

Accordingly, the Appellants that claim 1 is allowable and request that the rejection of claim 1 be withdrawn.

2. Claim 3 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 3 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive. Accordingly, the Appellants submit that claim 3 is allowable and request that the rejection of claim 4 be withdrawn.

3. Claim 4 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 4 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 where the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent. Accordingly, the Appellants submit that claim 4 is allowable and request that the rejection of claim 4 be withdrawn.

4. Claim 5 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 5 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic. Accordingly, the Appellants submit that claim 5 is allowable and request that the rejection of claim 5 be withdrawn.

5. Claim 6 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 6 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone. Accordingly, the Appellants submit that claim 6 is allowable and request that the rejection of claim 6 be withdrawn.

6. Claim 7 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 7 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al* do not teach or suggest the method of claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, a non-steroidal anti-rheumatic agent, an analgesic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof. Accordingly, the Appellants submit that claim 7 is allowable and request that the rejection of claim 7 be withdrawn.

7. Claim 8 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 8 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not each or suggest the method of claim 1 wherein the LHRH antagonist is administered starting in the early to mid follicular phase. Accordingly, the Appellants submit that claim 8 is allowable and request that the rejection of claim 8 be withdrawn.

8. Claim 9 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 9 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2 LRHR antagonist. Accordingly, the Appellants submit that claim 9 is allowable and request that the rejection of claim 9 be withdrawn.

9. Claim 10 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 10 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly does of about 3 to 10 mg per week. Accordingly, the Appellants submit that claim 10 is allowable and request that the rejection of claim 10 be withdrawn.

10. Claim 11 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 11 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily does of about 0.25 mg to 0.5 mg/day. Accordingly, the Appellants submit that claim 11 is allowable and request that the rejection of claim 11 be withdrawn.

11. Claim 12 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 12 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month. Accordingly, the Appellants submit that claim 12 is allowable and request that the rejection of claim 12 be withdrawn.

12. Claim 13 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 13 is at least allowable for reasons given above with respect to claim 1 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claim 1 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year. Accordingly, the Appellants submit that claim 13 is allowable and request that the rejection of claim 13 be withdrawn.

13. Claim 30 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 30 is at least allowable for reasons given above with respect to claims 1 and 3 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claims 1 and 3 wherein said contraceptive is an oral contraceptive. Accordingly, the Appellants submit that claim 30 is allowable and request that the rejection of claim 30 be withdrawn.

14. Claim 31 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 31 is at least allowable for reasons given above with respect to claims 1 and 8 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claims 1 and 8 wherein the LHRH antagonist is administered on cycle day one to three. Accordingly, the Appellants submit that claim 31 is allowable and request that the rejection of claim 31 be withdrawn.

15. Claim 2 is Not Obvious In View of The Cited Documents

The Appellants submit that, during prosecution on the merits, the examiner failed to present a prima facie case of obviousness under 35 U.S.C. §103(a). It is the Appellant's position that that Engel '145, either alone or in combination with Hodgen '884 and/or Nachtigall *et al.* fail to teach or suggest the Appellants' presently claimed invention (*i.e.*, fails to teach or suggest all of the claim limitations) of a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist wherein the LH-RH antagonist is administered in a dosage to achieve the estrogen serum concentration level between about 35 pg/ml and about 80 pg/ml.

The primary reference, Engel'145, simply discloses a kit comprising an initial dose of an LH-RH antagonist suitable for treatment of hormone dependent conditions, and at least one maintenance dose of the LH-RH antagonist. The kit is suitable for a combination treatment regiment in which an initial dose is followed by several maintenance doses. In contrast, the claimed invention is directed to a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment

for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

As admitted to by the examiner, Engel '145 does **not** specify either the time period or frequency of administration or the amounts of the LH-RH antagonist to achieve the estrogen serum level of between 35 and 80 pg/ml nor does the cited document teach or suggest any follow-up treatment or therapy with progestine/gestagens or androgens for further prevention of ovulation besides menstrual and endometrial bleeding to avoid re-occurrence of symptoms or new endometric. Additionally, an immediate follow-up therapy with non-steroidal anti-rheumatic agents or analgesics is also not disclosed or suggested in Engel '145.

The first secondary reference, Hodgen '884 does nothing to cure the deficiencies of Engel '145. The examiner cited Hodgen '884 as teaching administration of the GnRH antagonist such that the estrogen level between 35 and 45 pg/ml is achieved. Hodgen '884 actually **does** disclose that a 24 hour serum estradiol level in the range of 35 to 45 pg/ml can be achieved in monkeys by administering LH-RH antagonist. However, Hodgen does not give any dose range of the LH-RH antagonist. The dose has to be determined according to the results of an expensive and time consuming progesterone challenge test.

Furthermore, unlike the presently claimed invention (*i.e.*, short term induction), Hodgen '884 is directed to long-term treatment intervals, such as a number of years of therapy. See column 9, lines 3-6. The teachings of Hodgen '884 simply do not teach or suggest applicability of the long-term treatment study conducted on primates to a short-term induction treatment period. There is no teaching or suggestion from Hodgen '884 that an effective therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction may be achieved by a short 4-to 12 week induction treatment. Moreover, similarly to Engel '145, Hodgen '884 does not disclose any follow-up therapy.

In view of the foregoing, it is submitted that Engel '145 and Hodgen '884, either alone or in combination, neither teach nor suggest a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

The examiner further cited Nachtigall *et al.* as teaching use of Danazol, an oral contraceptive, for treatment of endometriosis. Once again, nothing in this reference suggests the claimed method, involving administering to a patient of LH-RH antagonist for a short-term induction period. Furthermore, while Danazol is useful in treating endometriosis, due to the occurrence of severe side effects, it is common knowledge that treatment of endometriosis with Danazol has been largely abandoned nowadays.

Oral contraceptives do not cure endometriosis. As disclosed on page 766, column 1, last paragraph of Nachtigall *et al.*, "there are few data to support the use of this class of drugs. No controlled or comparative trials have been performed to confirm efficacy, making this treatment approach at least acceptable of the medical therapies available." The reference, therefore, teaches away from use of oral contraceptives in treatment of endometriosis.

Non-steroidal anti-rheumatic agents and analgesics are discussed for the treatment of pain as well as of inflammation. *e.g.,* of patients with chronic adhesions or with low grade stages of the disease. These agents are not effective in curing patients with severe or chronic endometriosis, not even in the short term.

The examiner further states that it is *prima facie* obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose. It is well known in the art of therapeutic treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known

for the same purposes. Combination of pharmaceuticals often leads to serious side effects due to their potential interaction. Moreover, as discussed above, the invention is not directed to a combinatorial treatment, but rather to a follow-up treatment, and, therefore, the reasons for combining agents given by the examiner are simply not applicable to the claimed invention.

Also, according to the examiner's statement, optimization of parameters, such as dosage range, dosage frequency, and timing is obvious as being within the skill of the artisan. While routine minor adjustments of dosage and its frequency may well be within the skill of an ordinary artisan, reduction of treatment time from years of therapy as taught by the references to a maximum of three month periods, as claimed in the instant invention, can hardly fall within the meaning of "optimization." In fact, modifying the treatment regiments disclosed in the cited references to shorten them to 4 to 12 week induction treatments would render the treatment regimens disclosed in Engel '145 and Hodgen '884 unsatisfactory and non-useful for the intended therapeutic treatments.

It is, therefore, submitted that the references alone or in combination do not suggest the claimed therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment with subsequent termination of LH-RH antagonist administration.

The examiner admitted that Engel '145, the primary reference, teaches a two phase treatment of endometrial hyperplasia, using a dosage of 1 mg to 60 mg. The examiner also admitted that Engel '145 fails to teach the claimed time and frequency of cetrorelix administration, the claimed serum estrogen levels, or the follow up treatment with contraceptives, NSAIDs, analgesics, and certain androgens, as claimed. By contrast the claimed

treatment is a specified short term regiment, and is not limited to an initial high dose followed by maintenance doses. The present method requires a short term treatment during which serum estradiol levels are kept within the early follicular phase range of 35-80 pg/ml. In short, the examiner admitted that Engel '145 fails, at a minimum, to even suggest the claimed invention, and therefore is severely deficient as a reference for a rejection based upon 35 U.S.C. §103(a).

The examiner contended that a skilled artisan would combine the teachings of Hodgen '884 with Engel '145 to arrive at the claimed short-term therapy. The examiner stated that Hodgen '884 teaches treatment with an LH-RH antagonist for a period up to 97 days, which the examiner asserted is close to the claimed dosing frequency. Although the examiner cited no support in the specification for this assertion, it appears to the Appellants that the examiner is relying on the dosing data set forth in Table 1 of Hodgen '884.

The Appellants submit that the examiner has incorrectly analyzed the experimental data, and has ignored the sentence immediately following Table 1 in column 8, lines 55-58, wherein the data are described as evidence of the "utility of titering individualized GnRH ant [*sic*] doses to amenorrhea, while maintaining tonic ovarian estradiol secretion in a milieu suitable for extended therapeutic regimens." The actual treatment regimen of Hodgen '844, as previously noted to the examiner, suggests that 6 months is too short, and that a regimen lasting years is desirable.

The claims are not directed to a method requiring pre-therapeutic regimen titering. In fact, the specification teaches that the claimed method does **not** require titering of the dosage of LH-RH antagonists. Thus, it appears that the examiner is employing faulty logic in attempting to maintain the position that Hodgen '884 teaches something "close" to a 4-12 week treatment regimen for endometriosis.

Finally, the examiner continues to assert that a skilled artisan would read Nachtigall *et al.* to mean that various NSAIDs and contraceptives are useful in treating endometriosis. While

it is true that Nachtigall *et al.* teaches that oral contraceptives, GnRH analogs and testosterone derivatives are each separately useful in treating endometriosis, the cited document does not teach their combinations in treatment regimens (notwithstanding the fact that the present invention is directed, *inter alia*, to follow-up therapy). To the contrary, Hodgen '884 only teaches that combining surgical and medical (pharmacological) treatments may be desirable in managing the condition. The actual teachings of Nachtigall *et al.* rebut the examiner's assertion that it is *prima facie* obvious to combine the disclosed agents. Perhaps the examiner thinks such combinations are obvious, but those skilled in the art (Nachtigall *et al.*) did not seem to agree with this premise in 1994.

Nachtigall *et al.* does not teach nor suggest the follow up therapy required by the claims, or that more than one medical treatment is desirable. Nachtigall *et al.* certainly does not supplement the deficiencies of the combined teachings of Engel '145 and Hodgen '884 with respect to the claimed short-term treatment regimen administering an LH-RH antagonist for a period of about 4 to 12 weeks.

Accordingly, the Appellants submit that claim 2 is allowable and request that the rejection of claim 2 be withdrawn.

16. Claim 28 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 28 is at least allowable for reasons given above with respect to claim 2 and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* not teach or suggest the method of claim 2 wherein said estrogen serum concentration level is between about 45-75 pg/ml. Accordingly, the Appellants submit that claim 28 is allowable and request that the rejection of claim 28 be withdrawn.

17. Claim 29 is Not Obvious In View of the Cited Documents

The Appellants submit that claim 29 is at least allowable for reasons given above with respect to claims 2, 28, and for additional features recited therein.

The Appellants submit that Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.* do not teach or suggest the method of claims 1, 2, and 28 wherein said estrogen serum concentration level is about 50 to about 75 pg/ml. Accordingly, the Appellants submit that claim 29 is allowable and request that the rejection of claim 29 be withdrawn.

VI. CONCLUSION

For at least the reasons discussed above, it is respectfully submitted that the claims 1-13 and 28-31 are not obvious under 35 U.S.C. § 103(a) Engel '145 in view of Hodgen '884 and/or Nachtigall *et al.*

For the above reasons, the Appellanta respectfully requests this Honorable Board to reverse the rejection of the claims.

Respectfully submitted,
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VI. APPENDIX

PENDING CLAIMS

1. In the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction, the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, whereby subsequently the administration of the LHRH antagonist is ceased.

2. In the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction, the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, wherein the LHRH antagonist is administered in a dosage to achieve the estrogen serum concentration level between about 35 pg/ml and about 80 pg/ml, whereby subsequently the administration of the LHRH antagonist is ceased.

3. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive.

4. A method according to claim 1 where the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

5. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

6. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

7. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, a non-steroidal anti-rheumatic agent, an analgesic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

8. A method according to claim 1 wherein the LHRH antagonist is administered starting in the early to mid follicular phase.

9. A method according to claim 1 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2 LRHR antagonist.

10. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly does of about 3 to 10 mg per week.

11. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily does of about 0.25 mg to 0.5 mg/day.

12. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month.

13. A method according to claim 1 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

28. A method according to claim 2, wherein said estrogen serum concentration level is between about 45-75 pg/ml.

29. A method according to claim 28, wherein said estrogen serum concentration level is about 50 to about 75 pg/ml.

30. A method according to claim 3, wherein said contraceptive is an oral contraceptive.

31. A method according to claim 8, wherein the LHRH antagonist is administered on cycle day one to three.